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Clinical correlations of microstructural changes in progressive supranuclear palsy

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ABSTRACT

In patients with progressive supranuclear palsy (PSP), previous reports have shown a severe white matter (WM) damage involving supra and infratentorial regions including cerebellum. In the present study, we investigated potential correlations between WM integrity loss and clinical-cognitive features of patients with PSP. By using magnetic resonance imaging and diffusion tensor imaging with tract based spatial statistic analysis, we analyzed WM volume in 18 patients with PSP and 18 healthy controls (HCs). All patients and HCs underwent a detailed clinical and neuropsychological evaluation. Relative to HCs, patients with PSP showed WM changes encompassing supra and infratentorial areas such as corpus callosum, fornix, midbrain, inferior fronto-occipital fasciculus, anterior thalamic radiation, superior cerebellar peduncle, superior longitudinal fasciculus, uncinate fasciculus, cingulate gyrus, and cortico-spinal tract bilaterally. Among different correlations between motor-cognitive features and WM structural abnormalities, we detected a significant association between fronto-cerebellar WM loss and executive cognitive impairment in patients with PSP. Our findings, therefore, corroborate the hypothesis that cognitive impairment in PSP may result from both "intrinsic" and "extrinsic" frontal lobe dysfunction, likely related to cerebellar disconnection.

1. Introduction

Progressive supranuclear palsy (PSP) is a late-onset neurodegenerative disorder characterized by motor and cognitive deficits (Burn and Lees, 2002). Several clinical variants have been recently identified, differing in severity, clinical features, and preferred regions of detectable pathology (Williams and Lees, 2009). Cognitive dysfunction in patients with PSP is mainly characterized by attention, executive deficits, and verbal and nonverbal memory impairment with a relative preservation of recognition (Borroni et al., 2008; Brown et al., 2010; Donker et al., 2007). Patients' performance to frontal assessment battery (FAB) and phonological verbal fluency (pVF) tests has been demonstrated to be valuable in detecting early cognitive impairment in patients with PSP (Brown et al., 2010).

Previous structural imaging studies have revealed a widespread cortical and subcortical gray matter atrophy (Canu et al., 2011; Price et al., 2004; Whitwell et al., 2011a, 2011b) and a severe white matter (WM) damage, encompassing corpus callosum, fronto-temporo-parietal-occipital tracts, brainstem, and thalamic radiations (Agosta et al., 2012; Knake et al., 2010; Padovani et al., 2006; Saini et al., 2012). Moreover, cerebellar atrophy has been consistently reported in vivo (Agosta et al., 2010; Price et al., 2004) and postmortem studies (Kanazawa et al., 2009). These structural abnormalities may contribute to different PSP clinical phenotypes (Cordato et al., 2005; Paviour et al., 2006; Whitwell et al., 2011a, 2011b).

Based on our previous results (Giordano et al., 2013), highlighting the role of fronto-cerebellar gray matter atrophy in the pathogenesis of motor and cognitive impairment in 16 of the 18 patients enrolled in the present diffusion tensor imaging (DTI) study, we investigated clinical and cognitive correlations of WM damage in PSP. Therefore, the aims of the present study were (1) to

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Table 1
Demographic, clinical, cognitive[a], and imaging details of patients with PSP and HCs

	HCs (n = 18) mean ± SD	PSP (n = 18) mean ± SD	*p*
Age	64.5 ± 6.28	67.85 ± 1.35	0.2
Gender (M/F)	9/9	10/8	0.5
Right-handed	18	18	1
Education (y)	8.05 ± 2.73	8.4 ± 3.34	0.7
Disease duration (y)	—	3.38 ± 1.57	—
UPDRS (motor score)	—	29.88 ± 5	—
H&Y stage	—	3.26 ± 0.79	—
Daily levodopa dose (mg/die)	—	800 ± 224.30	—
PSIS/5	—	2.69 ± 1.18	—
PIGDs	—	11.05 ± 2.07	—
MMSE	28.15 ± 0.77	21.70 ± 3.41	<0.001
FAB	17.76 ± 0.43	8.76 ± 2.90	<0.001
pVF	31.88 ± 0.78	7.44 ± 4.66	<0.001
TPCT	10	5.18 ± 0.98	<0.001
BDI	5.82 ± 0.72	10.05 ± 3.47	<0.001
MRPI	7.40 ± 0.85	20.13 ± 4.32	<0.001
WMH volume, mL	0.34 (0–3.32)	3.15 (0–6.5)	<0.001

Key: BDI, Beck depression inventory scale; FAB, frontal assessment battery; HCs, healthy controls; H&Y stage, Hoehn & Yahr stage; MMSE, mini mental status examination; MRPI, magnetic resonance parkinsonism index; PIGDs, postural instability gait disturbance sub-score; PSIS/5, PSP saccadic impairment scale; pVF, phonological verbal fluency; SD, standard deviation; TPCT, ten-point clock test; UPDRS, unified Parkinson's disease rating scale; WMH, white-matter hyperintensity.
[a] Scores are age- and education-adjusted.

determine the spatial distribution of microstructural changes in patients with PSP compared with healthy controls (HCs); (2) to investigate potential correlations between WM integrity loss and clinical-cognitive features of patients with PSP.

2. Methods

2.1. Patients population

Eighteen patients with probable PSP, according to National Institute of Neurological Disorders and Stroke and the Society for PSP criteria (Litvan et al., 1996) and a group of 18 HCs were included in the study. HCs, matched to the mean characteristics of the PSP sample (age, sex, and years of education), with no previous neurologic or psychiatric diseases were also included in the study. Adjunctive inclusion criteria for patients with PSP were: a poor or absent response to levodopa and a magnetic resonance parkinsonism index >13.55 (Morelli et al., 2011). Gross anatomic magnetic resonance imaging (MRI) abnormalities and vascular lesions in strategic brain areas such as midbrain and basal ganglia were ruled out by an experienced neuroradiologist who evaluated MRI scans for each subject. The local Ethical Committee approved the study and all participants gave written informed consent, according to the Helsinki Declaration.

2.2. Clinical, motor, and neuropsychological assessments

All patients with PSP underwent a detailed clinical and cognitive evaluation. We recorded demographic data, disease history, and administered the Unified Parkinson's Disease Rating Scale (UPDRS) (Fahn and Elton, 1987). The following cognitive tests have been performed in both patients with PSP and HCs: the Mini Mental Status Examination (MMSE) for a global cognitive evaluation (Folstein et al., 1975); the FAB (Appollonio et al., 2005), to assess

Table 2
Regions of WM tissue loss in patient with PSP compared with HCs (all clusters were significant at $p < 0.05$ corrected for multiple comparisons)

Anatomic region	Side	MNI coordinates			DTI indices			
		x	y	z	FA	MD	RD	AD
Corpus callosum								
Body		0	−26	22	↙	↙	↙	↙
Genu		−3	26	5	↙	↙	↙	—
Splenium		5	−37	16	↙	—	↙	—
Cortico-spinal tract	L	−6	−27	−36	↙	↙	↙	↙
	R	21	−28	58	↙	↙	↙	↙
Anterior thalamic radiation	L	−8	−9	3	↙	↙	↙	↙
	R	7	−9	−4	↙	↙	↙	↙
Fornix	R	4	−12	13	↙	↙	—	↙
Inferior fronto-occipital fasciculus	L	−28	−72	−2	↙	↙	↙	↙
	R	29	38	3	↙	↙	↙	↙
Superior longitudinal fasciculus	L	−39	−14	30	↙	↙	↙	↙
	R	50	−5	27	↙	↙	↙	—
Anterior cingulate gyrus	L	−9	30	18	↙	↙	↙	—
	R	10	−37	32	↙	—	—	—
Uncinate fasciculus	L	−39	−1	−20	↙	↙	↙	↙
	R	27	13	−7	↙	↙	↙	↙
Midbrain		0	−26	−18	↙	↙	↙	↙
Superior cerebellar peduncles	L	−7	−41	−26	↙	↙	↙	↙
	R	7	−41	−26	↙	↙	↙	↙

Significant changes are represented by ↙ and — represents no changes.
Key: AD, axial diffusivity; DTI, diffusion tensor imaging; FA, fractional anisotropy; HCs, healthy controls; L, left; MD, mean diffusivity; R, right; RD, radial diffusivity; WM, white matter.